(c) disposing the pin assembly to align the vesicles at a first set of locations adjacent to a surface of the substrate without contacting the surface with the vesicles;

(d) contacting the loaded fluid to the surface of the substrate aligned with the vesicles to deposit a defined and controlled 0.2 to 20 nanoliter volume at each location, whereby an array of spots of material on the surface of the substrate is formed, such that spot-to-spot characteristics are reproducible in the array; and

(e) analyzing the array of material on the surface of the substrate by mass spectrometry.

REMARKS

A check for the fee for a 3 month extension of time accompanies this response. Any fee that may be due in connection with this application may be charged to Deposit Account No. 50-1213. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Claims 1-6, 9-34, 40-51 and 54-94 are pending in this application. Claims 1, 5, 31, 40 and 70 to more particularly point out and distinctly claim the subject matter that applicant regards as the invention by reciting that the methods deliver defined and controlled volumes to produce arrays with uniform spots by and the systems contain such arrays.

THE REJECTION OF CLAIMS 1-6, 9-34 AND 54-94 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-6, 9-34 and 54-94 under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for capillaries dispensing with the range of 0.2-2 nL, allegedly does not provide enablement for the vesicle to dispense in the "sub to low" range. This rejection is respectfully traversed.

While not conceding the propriety of the rejection, in the interest of advancing claims to issuance, the claims, as amended, recite that the volume 0.2 to 20 nanoliters, thereby rendering this rejection moot.

THE REJECTION OF CLAIMS 1-6, 9-34 AND 54-94 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1-6, 9-34 and 54-94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. While not conceding the propriety of the rejection, in the interest of advancing claims to issuance, the claims, as amended, recite that the volume 0.2 to 20 nanoliters, thereby rendering this rejection moot.

THE REJECTION OF CLAIMS 1-6, 9-34, 40-51, 54-69 and 70-101 UNDER 35 U.S.C. § 103(a)

Claims 1-6, 9-34, 40-51, 54-69 and 87-93

Claims 1-6, 9-34, 40-51, 54-69 and 87-93 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Tisone, U.S. Patent No. 5,743,960 ("Tisone") in view of Jespersen *et al.* or Li *et al.* because Tisone is alleged to teach a method for dispensing a material on a substrate "substantially similar to that as presently claimed." Tisone's method is alleged to comprise the steps of providing a vesicle having an interior chamber containing a fluid, disposing the vesicle adjacent to a first location on the surface of a substrate, controlling the vesicles to eject from the chamber a nanoliter volume of the fluid to dispense the fluid at the first location on the surface of the substrate, and moving the vesicle to a set of positions so that fluid is dispensed from the vesicle at each location of the set for forming an array of fluid material (figures 1, 6 and 7). Tisone is also alleged to teach that the method can be used to dispense sample fluids onto a diagnostic test strip for testing. It is acknowledged that Tisone does not teach or suggest the step of performing mass spectrometry analysis for the material. Jespersen *et al.* is cited for its teaching of detection of biomolecules by MALDI and allegedly improved detection limits by reduction in sample size, and Li *et al.* allegedly teaches deposition of small volume spots for analysis by TOF-MS.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art to have "provided the method and apparatus of applying nanoliter volumes" as taught by Tisone *et al.* and analyze it by mass spectrometry as taught

by Jespersen *et al.* and Li *et al.* in order to achieve an improvement in detection limits. This rejection is respectfully traversed.

Relevant law

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. § 103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed subject matter. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.* 732 F.2d 1572, 1577. 221 USPQ 929, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. *Stratoflex Inc. v Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 USPQ 1783 (Fed. Cir. 1992).

Also, it is impermissible to ignore the advantages, properties, utilities and unexpected results that flow from the claimed invention; they are part of the invention as a whole. *In re Sernaker*, 702 F.2d 989, 217 USPQ 1 (Fed. Cir. 1983). Unexpected properties must always be considered when determining obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. *In re Papesh*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

The claims

Claim 1 and dependents are directed to a method for forming an array of a sample material on a surface of a substrate and analyzing the sample material in the resulting array, by:

providing a vesicle that has an interior chamber containing a fluid comprising a solvent containing the sample material;

disposing said vesicle adjacent to a first location on said surface of the substrate without contacting the surface with the vesicle;

providing mechanical pressure to the interior of the vesicle to eject from said chamber **a defined and controlled 0.2 to 20 nanoliter volume** of the fluid to dispense said fluid at said first location of said surface of the substrate;

moving said vesicle to each of a set of positions adjacent to the surface of the substrate, whereby a defined and controlled sub to low nanoliter volume of fluid is dispensed at each location of said set forming **an array of spots of sample material on the substrate such that spot-to-spot characteristics are reproducible in the array**; and

performing mass spectrometry analysis of the sample material at each location of the array.

Claim 5 and dependents are directed to a method for forming an array of a sample material on a surface of a substrate and analyzing the sample material in the resulting array. In this method, a defined and controlled 0.2 to 20 nanoliter volume of solvent containing matrix material at said first location is dispensed, and after

a predetermined period of time, analyte material is dispensed to form a crystalline structure on at each locus of the substrate surface **such that spot-to-spot characteristics are reproducible in the array.**

Claim 25 is directed to a method for analyzing a material by producing an array that results from deposition of defined and controlled nanoliter volumes of fluid to form an array of the material **such that spot-to-spot characteristics are reproducible in the array**, and

performing mass spectrometry analysis for said material at each location of said array.

Claim 31 is directed to a system for forming an array of sample material. The system includes:

a vesicle having a distal end suitable for carrying a nanoliter of fluid;

a movable arm having a distal portion mounted to move said vesicle;

a controller for moving said arm to dispose said vesicle adjacent to a first location on said surface of the substrate and for controlling said vesicle **to deliver a defined and controlled 0.2 to 20 nanoliter volume of the fluid at said first location of said surface of the substrate**; and

a mass spectrometer for analyzing said material deposited on said surface of said substrate.

Claim 40 and dependents are directed to methods for dispensing sub to low nanoliter volumes of a material as an array onto the surface of a substrate by:

(a) providing an assembly having a plurality of vesicles arranged in the form of array for dispensing a liquid therefrom, wherein each vesicle has an interior chamber containing a fluid containing the material;

(b) aligning the vesicles at a first set of locations adjacent to the surface of the substrate without contacting the surface with the vesicles;

(c) using mechanical pressure, controlling each of the chambers to eject a defined and controlled 0.2 to 20 nanoliter volume of the fluid from each vesicle onto the surface of the substrate aligned with the vesicles, whereby an array spots

of the fluid is deposited on the surface of the substrate, such that spot-to-spot characteristics are reproducible in the array;

(d) providing the resulting substrate with the array of material deposited thereon to a mass spectrometer [for] and determining information representative of the composition of the deposited material.

Teachings of the cited references and differences from the instant claims

Tisone

Tisone teaches a reagent dispensing apparatus that has a positive displacement syringe pump in series with a solenoid valve dispenser. The pump is controlled by a stepper motor to provide an incremental quantity or continuous flow of reagent to the solenoid valve dispenser. The solenoid valve is opened and closed at a predetermined frequency and duty cycle to dispense droplets of reagent onto a target substrate at the metered flow rate.Tisone also teaches that its apparatus can be used for aspirating ("sucking") precise quantities of reagent or other liquids from a sample or reservoir. At column 11, lines 17-21, Tisone states:

> This mode may be used, for example, in a "suck and spit" operation whereby a precise quantity of fluid is aspirated from one vial containing a sample fluid and then dispensed into another vial or onto a diagnostic test strip for testing or further processing.

Tisone thus teaches an apparatus for dispensing single relatively large volumes on test strips or into vials. Tisone does not teach or even suggest deposition of defined and controlled volumes in arrays such that the such that spot-to-spot characteristics are reproducible in the array. Tisone does not teach or suggest analysis of such arrays by mass spectrometry nor does Tisone suggest selection of defined and controlled 0.2-20 nanoliter volumes nor that improved reproducibility for mass spectrometric analyses can be achieved by deposition of controlled and defined volumes in an array.

Tisone do teach Precise dispensing Col 17 line 65 Col 18 line 32

Jespersen *et al.* and Li *et al.*

Jesperson *et al.*

Jespersen *et al.* teaches the application of "picolitre" vials as a way to reduce the sample matrix volume for analysis of crude samples. Jespersen *et al.* teaches MALDI analysis of a small volume as way to lower the detection limit of MALDI analysis. Jespersen *et al.* does not teach or suggest depositing defined and controlled volumes to produce arrays of such sample material such that spot-to-spot characteristics are uniform. Jesperson *et al.* does not teach or suggest that such uniformity is a requisite for obtaining uniform spectra in high throughput formats.

Li *et al.*

Li *et al.* describes the analysis of single mammalian cell lysates using MALDI mass spectrometry. In the method described by Li *et al.*, a fused silica capillary is used to apply a volume of sample, which is determined by the length of the sample plug in the capillary, to a single location on the center of a MALDI probe precoated with a thin layer of matrix. The sample spot is always placed near the center of the probe using a microscope to position the sample spot in or near the center of the probe (p. 11662, rt. col., first full paragraph, lines 11-17).

Li *et al.* states that as little as 20 pl of sample solution can be accurately delivered on the matrix layer producing an ~100 μm diameter spot on the probe surface. The laser desorption beam is stated to be a 50 x 180 μm oval that is prealigned with the center of the probe surface. Although Li *et al.* states that the idea of microspot MALDI is to reduce the sample presentation surface with respect to the laser desorption site and ion acceptance volume in the mass spectrometer to improve sampling efficiency, Li *et al.* teaches that by rotating the sample probe, MALDI mass spectra are recorded from different areas in the sample spot.

Li *et al.* describes the method as a mass spectrometric approach for highly sensitive detection of small-volume protein samples such as are obtained from a lysate of a single cell. It is stated in Li *et al.* that the system provides attomole sensitivity for peptides and that further improvements of the sensitivity should be possible. The focus of the experiment described in Li *et al.* was to investigate the

sensitivity of mass spectrometric analysis of the small volumes of material obtain from a single cell. It is concluded that the work described in Li *et al.* illustrates that loading and analyzing a small-volume single cell is feasible by the microspot MALDI technique, and that the spectra and results shown are very reproducible for repeated preparations. Li *et al.* further states that the addition of several other features to this technique including quantitation, affinity separation, nanoliter or picoliter chemical and enzymatic reactions and tandem MS should further expand the usefulness of the mass spectrometric approach.

Neither Jesperson *et al.* nor Li *et al.* teaches or suggests the increase in reproducibility from spot-to-spot by delivery or deposition of defined and controlled volumes results in uniform spectra as shown in the DECLARATION of record.

Analysis

The Office Action fails to set forth a case of *prima facie* obviousness

The combination of teachings of Tisone with Li *et al.* or Jespersen *et al.* does not result in the instantly claimed methods

None of the cited references singly or in any combination thereof teaches or suggests delivery of a defined and controlled nanoliter (or subnanoliter) volumes onto a substrate and analysis of the resulting substrate by mass spectrometry.

As noted, Tisone *et al.* delivers large volumes, does not suggest analysis by mass spectrometry, does not suggest delivery of defined and controlled volumes to produce substrates with uniform spot-to-spot characteristics.

Jesperson *et al.* and/or Li *et al.* fail to cure these deficiencies. The mere fact that Li *et al.* and Jespersen *et al.* describe mass spectrometric analysis of a small volume of sample, does not, however, cure the defects of the Tisone reference to result in the instantly claimed methods and systems. Each of Jesperson *et al.* and Li *et al.* is directed to analysis of a small volume, but neither suggests an array in which defined and controlled volumes are deposited nor arrays of spots with uniform spot-to-spot characteristics. Jesperson *et al.* is concerned with the detection limits of proteins of MALDI-MS and Li *et al.* is directed to single cell analyses and detection of small volume samples.

In fact, Li *et al.* may be viewed as, in effect, teaching away from such. Li *et al.* states that only a single sample spot is applied to a probe and is always placed near the center of the probe. Li *et al.* does not teach or even suggest depositing more than a single spot of sample solution to anywhere except the center of a MALDI probe surface. Although Li *et al.* mentions that the spectra and results are reproducible for repeated single preparations, each being individually analyzed as a single spot on the probe, it does not teach or suggest a substrate containing an array of spots of sample solution wherein **the characteristics of each spot are highly reproducible within the array** which are particularly well suited for use for large-scale, high-throughput mass spectrometric analysis in applications, *e.g.*, DNA diagnostics, where accuracy and reproducibility are critical. Similarly, Jesperson *et al.* is directed to the use of picoliter vials, but does not teach or suggest deposition of a defined and controlled volume of material into an array of such vials, nor results derived therefrom.

Nowhere in Li *et al.* or Jespersen is an array of spots containing matrix material in an amount resulting from deposition of the material onto a substrate in defined and controlled sub- to low-nanoliter volumes taught or suggested where **the characteristics of each spot are highly reproducible within the array**. Therefore, the combination of teachings does not result in the instantly claimed methods and systems.

Unexpected properties

It is impermissible to ignore the advantages, properties, utilities and unexpected results that flow from the claimed invention; they are part of the invention as a whole.

The presently claimed methods and systems possess unexpected properties not taught or suggested by the cited references

THE DECLARATION OF KÖSTER

The unexpected properties of the presently claimed systems are illustrated in the DECLARATION of Köster pursuant to 37 C.F.R. §1.132. Dr. Köster and his colleagues conducted the experiments presented in the DECLARATION and in the paper Little *et al.*, which is attached to and part of the DECLARATION, as well as the above-described example in the application.

The results show that the sample array formed by deposition of uniform nanoliter volumes has properties that are not taught or suggested by the cited references. The DECLARATION shows that spot-to-spot reproducibility from microdispensed samples is superior to that achieved using samples prepared by conventional pipetting. The DECLARATION demonstrates that the sample array with low volume spot sized having the above-described properties contributes to the shortened spectrum acquisition time (Declaration, paragraph 9), increased detection sensitivity (Declaration, paragraph 10) and makes sample handling far more routine and amenable to automation (Declaration, paragraph 11). When the miniaturized automated sample dispensing was used in dispensing biological samples, *e.g.*, dispensing samples generated in a temperature-cycled PROBE reaction (Declaration, paragraphs 12-13), highly sensitive and accurate and reproducible (from spot-to-spot) analyses are achieved.

As a result the instantly claimed systems and methods when used for mass spectrometric analysis, as claimed, permit highly accurate and reproducible mass spectrometric analyses to be performed. By virtue of the small uniform spot size, there is a resulting high sample-to-sample uniformity of the sample spots. This eliminates difficulties associated with nonuniform analyte incorporation and translates to a high spectrum acquisition spectrum reproducibility and high speed spectrum acquisition.

None of the cited reference singly or in combination teaches or suggests that uniform spot size is a requisite mass spectrometric analyses of arrays of sample, nor that the result of such spot size leads to increased reproducibility in the results such that arrays of such spots can be used for high throughput analyses. Absent

such reproducibility, arrays of samples would not be a suitable for mass spectrometric analyses, such as high throughput DNA diagnostics and sequencing for which the instantly claimed systems are employed.

Therefore, the presently claimed systems and methods achieve results *i.e.*, the shortened spectrum acquisition time, increased detection sensitivity, greater reproducibility, routine sample handling and amenability to automation that are not taught or suggested by the cited references.

Claims 70-86 and 94

Claims 70-86 and 94 rejected under 35 U.S.C. §103(a) as being unpatentable over Ershow *et al.*, which teaches a tool for dispensing small volumes, in view of Jespersen *et al.* or Li *et al.* because Ershow *et al.* teaches a pintool apparatus and Jespersen *et al.* or Li *et al.* each teach the use of mass spectrometric analysis of small volumes.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art to have provided the method and apparatus of Ershow *et al.* and analyze it by mass spectrometry as taught by Jespersen *et al.* and Li *et al.* in order to achieve an improvement in detection limits.

The claims

Claim 70 and dependents are directed to methods for dispensing nanoliter volumes of a material as an array on the surface of a substrate and analyzing the material in the array, by:

(a) providing a pin assembly having a plurality of elongated vesicles arranged as an array for dispensing a liquid therefrom, wherein each vesicle comprises a solid shaft of material having an end for retaining a nanoliter volume of fluid;

(b) loading a defined and controlled nanoliter volume of fluid comprising a liquid material from a fluid source onto the end of the vesicles of the pin assembly;

(c) disposing the pin assembly to align the vesicles at a first set of locations adjacent to a surface of the substrate without contacting the surface with the vesicles;

(d) contacting the loaded fluid to the surface of the substrate aligned with the vesicles to deposit a defined and controlled 0.2 to 20 nanoliter volume at each location, whereby an array of spots of material on the surface of the substrate is formed, such that spot-to-spot characteristics are reproducible in the array; and

(e) analyzing the array of material on the surface of the substrate by mass spectrometry.

Analysis

As discussed with respect to the rejection above, none of these references, singly or in combination, teaches or suggests that increase in reproducibility achieved by deposition of small volumes for analysis by mass spectrometry.

Teachings of the cited references

Ershow *et al.* teaches a tool for transferring small volumes. Transfer is effected by using free surface end of a rodlike transferring element, which is maintained at essentially the dew point of the ambient air during the transfer. The device can include a plate-like base to which are affixed a plurality of rods such that the unfixed butt ends of the rods are coplanar. The device also includes a means for maintaining the temperature of the unfixed butt ends of the rods essentially equal to the dew point of the ambient air during transfer of the aqueous substance.

Ershow *et al.* does not teach or suggest that volumes dispensed must be controlled and defined to produce a substrate with uniform spots. It is directed to solving problems associated with evaporation and viscosity increases.

The teachings of Li *et al.* and Jespersen *et al.* are discussed as above.

Analysis

It is respectfully submitted that Ershow *et al.* and Jespersen *et al.* or Li *et al.*, whether alone or in combination, does not result in the instantly claimed methods. Ershow *et al.* does not teach or suggest the use of mass spectrometry for analysis of the materials deposited on a substrate by its device. Jespersen *et al.* is directed to an assessment of the detection limits of proteins by MALDI by delivering small

volumes into picoliter vials to assess the detection limits, and Li *et al.* is directed to analysis of crude lysates on a probe. Li *et al.* is not directed to analysis of a plurality of samples, and Jespersen *et al.* provides an approach to reducing sample/matrix volumes. Neither Jespersen *et al.* nor Li *et al.* suggests analysis of samples deposited by the device and methods of Ershow *et al.* by mass spectrometry. Therefore, neither Jespersen *et al.* nor Li *et al.* cures the deficiencies in the teachings of Ershow *et al.*, which fails to suggest analysis of samples by mass spectrometry.

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. *Stratoflex Inc. v Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 USPQ 1783 (Fed. Cir. 1992). In this instance, none of the cited references, teaches or suggests methods or systems for preparing substrates with uniform spots and analysis of the resulting substrates by mass spectrometry. Ershow *et al.* does not mention mass spectrometric analsyses, and each of Jespersen *et al.* and Li *et al.* is directed to methods completely different from those of Ershow *et al.* so that they do not suggest using the substrates of Ershow *et al.* for mass spectrometric analysis.

Furthermore, the combination of teachings of the references does not suggest the results that are achieved by depositing defined and controlled nanoliter volumes and analyzing the resulting arrays by mass spectrometry. As noted by the Examiner, Jespersen *et al.* suggests that decreasing the volume for analysis increases detection limits. This may be correct, but these are not the results achieved by the instantly claimed methods and systems. As shown in the DECLARATION, and discussed above, deposition of defined and controlled nanoliter and smaller volumes to produce substrates with uniform spots and analysis by mass spectrometry results in uniform mass spectra among the samples in the array.

The DECLARATION demonstrates that the sample array formed by nanoliter volume dispensing methods having the above-described properties contributes to the shortened spectrum acquisition time (Declaration, paragraph 9), increased detection sensitivity (Declaration, paragraph 10) and makes sample handling far more routine and amenable to automation (Declaration, paragraph 11). When the miniaturized sample dispensing methods were used in dispensing biological samples, *e.g.*, dispensing samples generated in a temperature-cycled PROBE reaction, highly sensitive and accurate analysis could be achieved. This permits use of such substrates in high throughput mass spectrometry formats. None of the cited references, singly or in any combination thereof teaches or suggests these results.

These results are not taught or suggested by any of Ershow *et al.*, Li *et al.* or Jespersen *et al.* singly or in any combination thereof. Therefore, the Examiner has failed to set forth a prima facie case of obviousness.

* * *

In view of the above remarks and the amendments and remarks of record, consideration and allowance of the application are respectfully requested.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: LITTLE et al.

Serial No.: 08/786,988

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For: SYSTEMS AND METHODS FOR PREPARING AND ANALYZING LOW VOLUME ANALYTE ARRAY ELEMENTS

Art Unit: 1743

Examiner: Bex, P.

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Stephanie Seidman

MARKED-UP CLAIMS

Please amend claims 1, 5, 25, 31, 40, 63, 64, 66 and 70 as follows:

1. (Thrice Amended) A method for forming an array of a sample material on a surface of a substrate and analyzing the sample material in the resulting array, comprising:

providing a vesicle that has an interior chamber containing a fluid comprising a solvent containing the sample material;

disposing said vesicle adjacent to a first location on said surface of the substrate without contacting the surface with the vesicle;

providing mechanical pressure to the interior of the vesicle to eject from said chamber a [sub to low nanoliter volume] defined and controlled 0.2 to 20 nanoliter volume of the fluid to dispense said fluid at said first location of said surface of the substrate;

moving said vesicle to each of a set of positions adjacent to the surface of the substrate, whereby a defined and controlled sub to low nanoliter volume of fluid is dispensed at each location of said set forming an array of spots of sample material on the substrate such that spot-to-spot characteristics are reproducible in the array; and

performing mass spectrometry analysis of the sample material at each location of the array.

5. (Twice Amended) A method for forming an array of a sample material on a surface of a substrate and analyzing the sample material in the resulting array, comprising:

providing a vesicle that has an interior chamber containing a fluid comprising a solvent containing material for deposition;

disposing said vesicle adjacent to a first location on said surface of the substrate without contacting the surface with the vesicle;

providing mechanical pressure to the interior of the vesicle to eject from said chamber a defined and controlled 0.2 to 20 nanoliter volume of the fluid to dispense solvent containing matrix material at said first location of said surface of the substrate, wherein the matrix material is for matrix-assisted laser desorption mass spectrometry;

waiting a predetermined period of time to allow the solvent containing the matrix material to evaporate on the surface of the substrate thereby depositing the matrix material on the surface;

moving said vesicle to each of a set of positions adjacent to the surface of the substrate, whereby a defined and controlled 0.2 to 20 nanoliter volume of fluid is dispensed at each location of said set forming an array of spots of matrix material on the substrate; and

ejecting a nanoliter volume of fluid containing an analyte material onto said evaporated matrix material at each locus of the array to dissolve with said matrix material and to form a crystalline structure on at each locus of the substrate surface such that spot-to-spot characteristics are reproducible in the array;

performing mass spectrometry analysis of the sample material at each location of the array.

25. (Amended four times) A method for analyzing a material, comprising:

providing a vesicle comprising a fluid containing the material in a solvent;

disposing said vesicle adjacent to a first location of a surface of a substrate without contacting the surface with the vesicle;

delivering a defined and controlled [sub to low] nanoliter volume of the fluid at the first location of said surface of the substrate;

moving said vesicle to a second position next to the first location on said surface of the substrate to dispense a defined and controlled [sub to low] nanoliter volume of said material along an array of locations on said substrate surface to form an array of the material such that spot-to-spot characteristics are reproducible in the array; and

performing mass spectrometry analysis for said material at each location of said array.

31. (Thrice Amended) A system for forming an array of a sample material on a surface of a substrate and analyzing the sample material in the array, comprising:

a vesicle having a distal end suitable for carrying a nanoliter of fluid;

a movable arm having a distal portion mounted to move said vesicle;

a controller for moving said arm to dispose said vesicle adjacent to a first location on said surface of the substrate and for controlling said vesicle to [provide a] deliver a defined and controlled [sub to low] 0.2 to 20 nanoliter volume of the fluid at said first location of said surface of the substrate; and

a mass spectrometer for analyzing said material deposited on said surface of said substrate.

40. (Thrice Amended) A method for dispensing sub to low nanoliter volumes of a material as an array onto the surface of a substrate, comprising the steps of:

(a) providing an assembly having a plurality of vesicles arranged in the form of array for dispensing a liquid therefrom, wherein each vesicle has an interior chamber containing a fluid containing the material;

(b) aligning the vesicles at a first set of locations adjacent to the surface of the substrate without contacting the surface with the vesicles;

(c) using mechanical pressure, controlling each of the chambers to eject a defined and controlled [sub to low] 0.2 to 20 nanoliter volume of the fluid from each vesicle onto the surface of the substrate aligned with the vesicles, whereby an array

spots of the fluid is deposited on the surface of the substrate, such that spot-to-spot characteristics are reproducible in the array;

(d) providing the resulting substrate with the array of material deposited thereon to a mass spectrometer [for] and determining information representative of the composition of the deposited material.

63. A substrate of claim [62] 40, wherein the material further comprises a nucleic acid.

64. The substrate of claim [62] 40 that comprises a hydrophilic flat surface.

66. The substrate of claim [62] 40 that comprises silicon.

70. (Thrice Amended) A method for dispensing nanoliter volumes of a material as an array on the surface of a substrate and analyzing the material in the array, comprising the steps of:

(a) providing a pin assembly having a plurality of elongated vesicles arranged as an array for dispensing a liquid therefrom, wherein each vesicle comprises a solid shaft of material having an end for retaining a nanoliter volume of fluid;

(b) loading a nanoliter volume of fluid comprising a liquid material from a fluid source onto the end of the vesicles of the pin assembly;

(c) disposing the pin assembly to align the vesicles at a first set of locations adjacent to a surface of the substrate without contacting the surface with the vesicles;

(d) contacting the loaded fluid to the surface of the substrate aligned with the vesicles to deposit a defined and controlled 0.2 to 20 [sub to low] nanoliter volume at each location, whereby an array of spots of material on the surface of the substrate is formed, such that spot-to-spot characteristics are reproducible in the array; and

(e) analyzing the array of material on the surface of the substrate by mass spectrometry.